Febrile Neutropenia in Cancer Patients: Microbiology and Empirical Antibiotic Therapy

Mustafa W, Pattharachayakul S, Mahattanadul S.
Faculty of Pharmaceutical sciences, Prince of Songklha University
Hatyai,Thailand.

Chusi S.
Faculty of Medicine, Prince of Songkla University
Hatyai,Thailand.

Abstract--This study was conducted to evaluate the empirical antibiotic therapy for febrile neutropenic patients, patterns of bacterial isolates and their drug resistance.
Method: It was a retrospective study; data of the patients admitted to the university hospital from 1/1/2010 to 1/6/2012 was evaluated retrospectively. ICD-10 for Cancer patients was used to locate the HN of oncology patients. Then Data for all of these patients was reviewed according to our inclusion criteria to select our sample population.
Results: A total of 272 microorganisms were isolated during the study period. Gram-negative bacteria accounted for 73.5% of organisms, while gram-positive organisms accounted for 21.6% of the total isolates. Ninety-three (48.9%) episodes were found to have inappropriate empirical antibiotic therapy. Bacterial isolates of 40 episodes were found to be resistant against the prescribed therapy, which is the 43.0% of the all episodes identified with inappropriate therapy. Thirty episodes (32.25%) were found to have delay in the empirical therapy and for remaining 23 episodes 24.73%, no fungal therapy was prescribed after continuous episode of febrile neutropenia for 7 days.
Conclusion: Gram-negative organisms are the predominant organisms in adult febrile neutropenic patients at our institute. Initial empirical therapy with piperacillin/tazobactam seems appropriate to cover most gram-negative pathogens, but considering high resistance of *Klebsiella pneumoniae*, other antipseudomonal b-lactam agent with no resistance should be considered. If fever does not settle after 4-7 days of antibiotic treatment, anti-fungal therapy should be added.

Keywords: febrile neutropenia; empirical therapy; infection; resistance patterns; bacterial isolates.

I. INTRODUCTION

Neutropenia is the single most important predisposing factor to infection in the patient with cancer and infection is the most common cause of death in the theses patients. Weissv RV *et al.* (2003) conducted a retrospective study in 7 large states of America, and found that among the cancer identified in 537,606 cases. Infection and neutropenia were identified in 2,060,749 and 54,439 cases, respectively.[1] Studies have also reported that 48% to 60% of patients admitted with febrile neutropenia do have infection[2]. Febrile neutropenia is costly in terms of morbidity, mortality and associated financial expenditure. These infections can be life threatening and increase both the morbidity and mortality.[3–6]

Patients with febrile neutropenia are at risk of life threatening sepsis, and therefore require immediate empirical antibiotic therapy. Infections in the neutropenic patient can be rapidly fatal if not managed properly. Appropriate and in time therapy is a key factor for the management of febrile neutropenic patients. Efforts should be done to improve the appropriateness of the empirical therapy or to find the other factors, which can influence the response of empirical therapy or patient clinical outcome.

Selection of appropriate empirical therapy for febrile neutropenic patients is vital for good clinical outcome of the patient. Patterns of infection and resistance may vary time-to-time and institution-to-institution. The choice of which antibiotic(s) to use needs to be established as a local policy, in consultation with the clinical teams managing patients on chemotherapy, and in accordance with local patterns of infection and resistance.

Over the past decade there has been a considerable change in the spectrum and antibiotic susceptibility patterns of pathogens causing infection in febrile neutropenic patients. Additionally use of broad-spectrum antibiotics has resulted in emergence of multi drug resistant gram negative and gram-positive bacteria. Therefore detection of epidemiological and resistance patterns shifts requires frequent monitoring and surveillance, particularly at centers treating large numbers of patients, where institutional differences can be substantial.

The main objective of this study was to highlight FN as a serious complication of chemotherapy, evaluate the empirical antimicrobial therapy, and to have an insight into the spectrum and the trend in antimicrobial susceptibility pattern of febrile neutropenic patients.

II. MATERIALS AND METHODS

This was a retrospective medical record review at Songklanagarind hospital, a large teaching hospital in southern Thailand. Data for all the oncology patients diagnosed with febrile neutropenia during the decided study period from 1/1/2010 to 1/6/2012 was reviewed. The Patient population consisted of adults (18years or above) with acute and chronic leukemia, lymphoma and solid tumors. Patients were included if they had fever greater than 38.3^{o}C on one occasion or >38.0^{o}C sustained for one hour and with an absolute neutrophil count of less than 500 cells/ microL and had

positive cultures result. Inappropriate therapy was defined by three different criteria.

- The bacterial isolate is not susceptible to the antimicrobial therapy.
- Administration of empirical antibiotic after 24 hrs of detection of temperature >38.3°C.
- Empirical therapy for fungus has not been started for patients having persistent fever after 4-7 days of antimicrobial therapy.

SPSS Version 16 was used for data compilation and calculation.

III. RESULTS

As described earlier it was a retrospective study, based on set criteria 580 potentially eligible patients were selected during the time period of 1/1/2010 to 1/6/2012. Two hundred and eight episodes of febrile neutropenia from 155 patients were selected to be included in the study. The mean age of the final cohort was 46.2 (range, 18 - 78) years. Table 1 shows the characteristics of all the patients included in the study.

Among 208 episodes majority (151, 72.6%) were caused by gram-negative microorganisms. Gram-positive organisms were responsible of 26 episodes (12.4%). 20 episodes (10.5%) were caused from multiple organisms including both gram positive & negative organisms. Eleven episodes (5.3%) were caused by organisms from fungal origin. In total 272 microorganisms were isolated from the 208 episodes including all febrile episodes caused by single and multiple organisms. Out of 272, 200 (73.5%) were gram negative and 59 (21.6%) were considered to be gram positive. Among gram-negative bacteria, *Escherichia coli* with the percentage of 21.6% remained a predominant organisms and *Enterococci species* with percentage of 7.3 % was most frequently seen bacteria from gram-positive bacteria. Frequencies of different individual microorganism are given in table 2.

Among febrile episodes from sterile sites, all episodes with the percentage of 139 (66.82%) were with bacteremia, and the remaining 69 (33.12%) were from unsterile sites. Among them urinary tract with the percentage of 40 19.23% was the second most site of infection, followed by gastrointestinal tract, chest and others with the percentages of 12 (5.78%) 11 (5.28%) and 6 (2.88%) respectively.

TABLE I. CHARACTERISTICS OF PATIENTS ADMITTED WITH FEBRILE NEUTROPENIA DURING STUDY TIME PERIOD.

Characteristics	All *(n)*
Number of episodes	208
Gender F/M	128/80
Type of cancer	
Solid	113
Liquid	95
vasopressors Use Yes/NO	73/135
Neutropenia level	
Moderate >100/microL	28
Sever <100/microL	180
Bactermia Yes/No	140/68
AKI* Yes/No	34/174

*Acute kidney Injury

Resistance patterns of isolated organisms during the study were also evaluated. *E.coli* and *Klebsiella pneumoniae* with the aggregate percentage of 41.1% (112) were the two most frequently isolated microorganisms. Out of total 112 isolates 26 (23.2%) were found to produce extended spectrum betalactamase (ESBL). Imipenem and piperacillin/tazobactam were the most frequently used antibiotics and either of those were prescribed to all those 26 patients, and 9 isolates (34.6%) were found to be resistant to piperacillin/tazobactam while only 2 (7.6%) were found to be resistant to imipenem. Resistance patterns of most frequently isolated organisms are shown in table 3.

According to the defined criteria 93 out of 208 episodes (44.5%) were found to have inappropriate empirical antibiotic therapy. Bacterial isolates of 40 episodes were found to be resistant against the empiric prescribed therapy, which accounted for 43.0% of the all episodes indentified with inappropriate therapy. Thirty episodes (32.25%) were found to be delayed in the empirical therapy and for the remaining 23 episodes (24.73%), no fungal therapy was prescribed after continuous episode of febrile neutropenia for 7 days.

TABLE II. SPECTRUM OF GRAM POSITIVE AND NEGATIVE ORGANISMS ISOLATED.

Microorganism	No. of isolates	Percentage
Escherichia coli	59	21.6%
Klebsiella pneumoniae	53	19.4%
Pseudomonas aeruginosa	38	13.9%
Proteus mirabilis	13	4.7%
Enterococci species	20	7.3%
Streptococcus species	15	5.5%
Staphylococcus aureus	10	3.6%
Candida species	12	4.4%

IV. DISCUSSION

Bacterial etiology is often unidentified at the onset of infection. Awareness of the prevalence of causative bacteria in neutropenic patients with fever is important since timely adequate antimicrobial therapy is of vital importance. The epidemiology of bacteraemia in neutropenic cancer patients has changed[7]. Published studies by the International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer (IATCG-EORTC) have demonstrated the changing epidemiology over the past 3 decades.

Gram-negative bacteria (GNB) caused approximately 70% of monomicrobial bacteraemia in the 1970s, but the situation was entirely overturned by the late 1980s and 1990s, with gram-positive organisms causing approximately 70% of the episodes[8-9]. But recent studies show that trend is again changed to gram-negative organisms [10-11]. The spectrum of bacterial isolates in our study is similar to what has been reported in other studies. Two hundred (73.5%) organisms were gram negative and 59 (21.6%) were gram-positive bacteria. Among gram-negative bacteria, *E.coli* with the percentage of 21.6% remained predominant organisms.

Modification of antibacterial therapy is a reality in clinical practice in the treatment of febrile neutropenia. Many studies have reported various response rates to empirical therapy from 50 -70% [12]. One of the reasons to low response to empirical therapy can be inappropriate therapy, so we have tried to evaluate the empirical antimicrobial therapy and found out that 93 (44.5%) patients were prescribed with inappropriate therapy. According to IDSA empirical antifungal coverage should be considered in patients who have persistent fever after 4–7 days of a broad-spectrum antibacterial regimen. Twenty-three patients (24.73%) were not prescribed with fungal therapy after continuous episode of febrile neutropenia for 7 days, in addition to changes in combination broad-spectrum antibiotics, starting antifungal therapy would be the appropriate response.

Bacterial isolates of 40 patients (43.0%) were found to be resistant against the prescribed therapy. At our institution, piperacillin/tazobactam is considered as a favorable choice and it is one of the most commonly prescribed antibiotics to the febrile neutropenic patients, but we have found high resistance (24.5%) to piperacillin/tazobactam in *Klebsiella pneumonia*, which is the second most commonly found organism in our study. Other anti-pseudomonal beta-lactam agents, such as carbapenem (meropenem or imipenem) with no resistance should be considered.

A large proportion of the patients were found to be prescribed with inappropriate therapy, but the issue of effect of inappropriate therapy on the clinical outcome of the patient is still need to be addressed, taking length of stay and mortality as a parameter for clinical outcome, we have planned to compare the data from the patients of this study. Episodes from both groups, with appropriate and inappropriate therapy will be included in the study.

TABLE III. RESISTANCE PATTERNS OF MOST FREQUENTLY ISOLATED ORGANISMS

Antibiotic	*E.coli*		*K. pneumoniae*		*P. aeruginosa*		ANTIBIOTIC	*Enterococci*	
	n=59	%	*n=53*	%	*n=38*	%		*n=20*	%
Imipenem	0	0	0	0	9	23.68	Imipenem	7	35.0
Ertapenem	0	0	0	0	-	-	Ampicillin	6	30.0
Meropenem	1	1.69	0	0	5	13.15	Gentamicin	7	35.5
Piperacillin/ tazobactam	2	3.38	13	24.5	3	7.89	Vancomycin	0	0
Ceftazidime	15	25.42	16	30.1	1	2.63	Penicillin	9	45.0
Ceftriaxone	15	25.42	16	30.1	-	-	-	-	-
Amikacin	0	0	0	0	0	0	-	-	-
Ciprofloxacin	23	38.98	21	39.62	2	5.26	-	-	-
Gentamicin	9	15.25	9	16.98	1	2.63	-	-	-
Cotrimoxazole	27	45.76	23	43.39	-	-	-	-	-
Colistin	0	0	0	0	0	0	-	-	-

REFERENCES

[1] Caggiano V, Weiss R. V, Rickert T. S, Linde-Zwirble W. T. Incidence, Cost and mortality of febrile neutropenia hospitalization (FNH) associated with chemotherapy. Cancer.2005 May 1;103(9):1916-24.

[2] Butt T, Afzal RK, Ahmed RN, Salman M, Mahmood A, Anwar M. Bloodstream infections in febrile neutropenic patients: bacterial spectrum and antimicrobial susceptibility pattern. J Ayub Med Coll Abbotabad 2004;16(1):18–22.

[3] Burney IA, Farooqui BJ, Siddiqui T, Khurshid M. The spectrum of bacterial infections in febrile neutropenic patients: effect on empiric antibiotic therapy. J Pak Med Assoc 1998;48:364–7.

[4] Khan MA, Siddiqui BK, Shamim A, Yousaf MA, Ahmad U, Zakiullah N. Emerging bacterial resistance patterns in febrile neutropenic patients: experience at a tertiary care hospital in Pakistan. J Pak Med Assoc 2004;54:357–60.

[5] Irfan S, Idress F, Mehraj V, Habib F, Adil S, Hasan R. Emergence of carbapenem resistant gram negative and vancomycin resistant gram positive organisms in bacteremic isolates of febrile neutropenic patients: a descriptive study. BMC Infectious Diseases 2008;8:80.

[6] Cattaneo C, Quaresmini G, Casari S, Capucci MA, Micheletti M, Borlenghi E. Recent changes in bacterial epidemiology and the emergence of fluoroquinolone-resistant Escherichia coli among patients with hematological malignancies: results of a prospective study on 823 patients at a single institution. J Antimicrob Chemother 2008;61:721–8.

[7] Oppenheim BA. The changing pattern of infection in neutropenic patients J Antimicrob Chemother 1998; 41 (Suppl D): 7-11.

[8] Klastersky J. Science and pragmatism in the treatment and prevention of neutropenic infection. J Antimicrob chemother 1998; 41 (Suppl D): 13-24.

[9] EORTC, Schimpff SC, Gaya H, Klastersky J, Tattersall MH, Zinner SH. Three antibiotic regimens in the treatment of infection in febrile granulocytopenic patients with cancer. The EORTC International Antimicrobial Therapy Project Group. J Infect Dis 1978; 137: 14-29.

[10] Sigurdardottir K, Digranes A,Harthug S, Nesthus I, Tangen JM, Dybdahl B.et al. A multi-centre prospective study of febrile neutropenia in Norway: microbiological findings and antimicrobial susceptibility. Scand J Infect Dis. 2005;37(6-7):455-64.

[11] Roongpoovapatr, Suankratay C. Causative pathogens of fever in neutropenic patients at King Chulalongkorn Memorial Hospital. J Med Assoc Thai. 2010 Jul;93(7):776-83.

[12] Shamsi T.S, Farzana T, Ansari S.H, Ahmed A, Ishaque A. Febrile Neutropenia in Haematological Disorders: a Single Centre review of Antibiotic Policy and the Outcome. JPMA 2003;53:190-193.